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Poor cardiorespiratory fitness is a risk factor for sepsis in patients awaiting liver transplantation

Matthew P. Wallen, PhD[1], Aidan J. Woodward, MBBS[2,3], Adrian Hall, MBBS[4], Tina L. Skinner, PhD[1], Jeff S. Coombes, PhD[1], Graeme A. Macdonald, MBBS PhD[2,3,5]

[1] Centre for Research on Exercise, Physical Activity and Health (CRExPAH), School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Queensland, Australia

[2] School of Medicine, The University of Queensland, Brisbane, Queensland, Australia

[3] Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia

[4] Department of Anaesthesia, Princess Alexandra Hospital, Brisbane, Queensland, Australia

[5] Translational Research Institute, Brisbane, Queensland, Australia

Corresponding Author:

Graeme A. Macdonald, MBBS, PhD, FAASLD

Senior Staff Specialist and Associate Professor of Medicine

Department of Gastroenterology and Hepatology

The Princess Alexandra Hospital, 199 Ipswich Rd, Woolloongabba, Queensland, 4011, Australia

Email: g.macdonald@uq.edu.au

Telephone: +61 (7) 3176 2613, Fax: +61 (7) 3176 5111

AUTHORSHIP PAGE

Authorship:

M.W. conceived and designed the research, performed and analysed the data, and wrote the article.

A.W. performed data collection, contributed to writing and revised the article.

A.H. performed data collection and revised the article.

T.S. contributed to writing and revised the article.

J.C. conceived and designed the research, advised on the research performance, contributed to writing and revised the article.

G.M. conceived and designed the research, advised on the performance of the research and revised the article.

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ABBREVIATIONS

CPET, cardiopulmonary exercise test

CT, computed tomography

HCC, hepatocellular carcinoma

MELD-Na, model of end stage liver disease, incorporating serum sodium

SATI, subcutaneous adipose tissue index

SMI, skeletal muscle index

VATI, visceral adipose tissue index

$\dot{V}E$, minute ventilation

$\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide

$\dot{V}E/\dot{V}O_2$, ventilatory equivalents for oxygen

$\dot{V}O_2$, volume of oxygen

$\dot{V}CO_2$, volume of carbon dioxide

VT, ventilatory threshold

ABSTRACT

Background: Patients with advanced liver disease are at increased risk of infection and other complications. A significant proportion of patients also have poor fitness and low muscle mass. The primary aim of this study was to investigate if cardiorespiratory fitness and body composition are risk factors for sepsis and other complications of advanced liver disease.

Methods: Patients being listed for liver transplantation underwent cardiopulmonary exercise testing to determine ventilatory threshold (VT). Computed tomography was used to measure skeletal muscle and subcutaneous and visceral adipose tissue indexes. All unplanned hospital admissions, deaths or delistings prior to transplantation were recorded.

Results: Eighty-two patients [aged 55.1 (50.6–59.4) years, median (interquartile range); male 87%] achieved a median VT of 11.7 (9.7–13.4) $mL \cdot kg^{-1} \cdot min^{-1}$. Their median MELD-Na score was 18 (14–22); and 37 had hepatocellular carcinoma. There were 50 admissions in 31 patients; with 16 admissions for sepsis in 13 patients. Patients with sepsis had a significantly lower VT [sepsis 9.5 (7.8–11.9), no sepsis 11.8 (10.5–13.8) $mL \cdot kg^{-1} \cdot min^{-1}$; P=0.003]. No body composition variables correlated with sepsis, nor were there any significant associations between VT and unplanned admissions for other indications. Multivariate logistic regression demonstrated that VT was independently associated with a diagnosis of sepsis (P=0.03). Poisson regression revealed that VT was a significant predictor for the number of septic

episodes (P=0.02); independent of age, MELD-Na score, hepatocellular carcinoma diagnosis, presence of ascites, and beta-blocker use.

Conclusion: Poor cardiorespiratory fitness is an independent risk factor for the development of sepsis in advanced liver disease.

INTRODUCTION

Cardiopulmonary exercise testing (CPET) is recognised as the gold-standard assessment of cardiorespiratory fitness. Several large-scale cohort studies in healthy populations have shown a correlation between low cardiorespiratory fitness (measured as maximal oxygen consumption ($\dot{V}O_2max$)) and adverse cardiometabolic events. Indeed, cardiorespiratory fitness appears to be a stronger predictor than obesity for all cause morbidity and mortality [1-3].

Patients with advanced liver disease often have poor cardiorespiratory fitness compared to sedentary but otherwise healthy, control subjects [4,5]. During CPET in patients with advanced liver disease, $\dot{V}O_2max$ may not be achieved due to peripheral fatigue resulting in an inability to attain a plateau in oxygen consumption despite an increase in exercise intensity (the criteria for maximal $\dot{V}O_2max$). The ventilatory threshold (VT) is a submaximal marker of cardiorespiratory fitness assessed during a CPET. It is defined as the point at which there is a nonlinear increase in ventilation with an increase in workload and is associated with the onset of increased anaerobic metabolism [6]. Several investigations have highlighted the importance of VT as a peri-transplant risk stratification tool [7-9], likely because the VT reflects available cardiorespiratory reserve to deal with the augmented tissue oxygen demand from systemic inflammation after surgery [10].

Sepsis is a major cause of morbidity and mortality in patients with advanced liver disease. Approximately 1-third of patients with cirrhosis admitted to hospital will have a bacterial infection [11-13]. Importantly, patients with cirrhosis hospitalized with

sepsis have a fourfold increased risk of dying within 1 year of developing these infections [14]. Sarcopenic obesity [15] and excessive visceral adipose tissue deposits [16] appear to predispose this cohort to sepsis. Tissue demand for oxygen is increased in sepsis, in part due to altered oxygen extraction [17], and hence cardiorespiratory fitness may impact on outcomes in sepsis. However, the relationship between a formal assessment of cardiorespiratory fitness and sepsis is yet to be established.

The aim of this study was to determine if VT is independently associated with sepsis and other complications of advanced liver disease in patients awaiting liver transplantation. Additionally, we sought to determine the relationships between VT, central adiposity, muscle mass and hospitalizations in this population.

MATERIALS AND METHODS

This was a retrospective cohort analysis of consecutive patients from October 2012 to June 2015 at a single study center (The Princess Alexandra Hospital, Woolloongabba, Queensland, Australia). All patients included in the analysis were listed for liver transplantation and had performed CPET and undergone a computed tomography (CT) scan prior to listing. Metro South Hospital and Health Services District and The University of Queensland's Human Research Ethics Committees granted ethical approval for the study (Approval numbers: HREC/14/QPAH/714; HMS13/1210). A waiver of consent to assess patient medical records was obtained under the Queensland Government Public Health Act. Patients were excluded from the study if they were less than 18 years old; diagnosed with underlying cholestatic liver disease; had previously received a liver transplant; listed for dual organ transplantation; and/or did not achieve VT during CPET.

Clinical data collection

Patient medical records were retrospectively examined for demographic (age, sex) and clinical factors at the time of the CPET [aetiology of liver disease (viral, alcohol, other); model of end-stage liver disease (MELD)-Na score; diagnosis of hepatocellular carcinoma (HCC); presence of ascites and gastroesophageal varices; and the use beta-blockers]. Laboratory parameters recorded at baseline included serum sodium, creatinine, bilirubin, albumin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and platelet count (**Table 1**).

The diagnosis of sepsis was assessed from the time of transplant listing until death, delisting, or liver transplantation. One author (AW) reviewed all hospital admissions for the cohort and confirmed reason for admission, including the diagnoses of sepsis requiring hospital admission, which was defined per international consensus guidelines [18]. Briefly, sepsis was diagnosed on the basis of a) documented infection induced by a microorganism and b) physical and/or laboratory signs of systemic inflammation in response to infection [18]. Each episode of sepsis was considered clinically significant as the patients required hospital admission and the administration of antibiotics.

Cardiopulmonary exercise testing (CPET)

In the study center, a CPET is performed routinely to assist with risk stratification prior to liver transplant surgery. All tests were performed on an upright cycle ergometer (Lode Corival, Groningen, Netherlands) with continuous gas exchange analysis and 12-lead electrocardiography (Ultima CardiO_2, MGC Diagnostics, St.

Paul, MN, USA). Patients adhered to pretest procedures as per the position statement by the American Thoracic Society and American College of Chest Physicians for Cardiopulmonary Exercise Testing, and were advised to maintain their usual medication dosages prior to CPET, including beta-blocker prophylaxis [19]. Standard calibration of gas analyzers (2 point calibration against 2 gravimetric gas standards: 21% oxygen, balance nitrogen and 5% carbon dioxide/ 12% oxygen, balance nitrogen) and volume (Hans Rudolph™ 3L calibration syringe) were performed as per manufacturer's recommendations.

Patients performed the CPET with breath-by-breath gas analysis. Testing was ceased if patients satisfied any indications for exercise termination (eg, ischemic electrocardiography changes; oxygen desaturation to ≤ 80% accompanied by signs and symptoms of severe hypoxemia) [19]. VT was determined using the modified V-slope method included in the BreezeSuite software (MGC Diagnostics, St. Paul, MN, USA), as the $\dot{V}O_2$ value corresponding with the nonlinear increase in the $\dot{V}O_2$-$\dot{V}CO_2$ slope. This value was confirmed using the ventilatory equivalents method, where VT was selected at the time-point consistent with the first continual increase in the ventilatory equivalents of VO_2 ($\dot{V}E/\dot{V}O_2$), with no consistent increase in the ventilatory equivalents for $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) [20,21]. A physician supervised the CPET (AH) and performed the analysis with the lead investigator (MW).

Computed Tomography (CT) analysis of muscle mass and central obesity

CT scanning was performed as part of standard liver transplant assessment prior to listing. Body composition data was obtained from a transverse CT image at the third lumbar vertebrae using ImageJ software (National Institute of Health, Bethesda, MD,

USA). All images were analysed by a single observer (AW) who was blinded to the CPET results, and who cross-validated 10 images with a radiologist with minimal interobserver variability (intraclass coefficient = 0.99). Tissue segmentation was performed using Hounsfield unit thresholds of -29 to +150 for muscle and -190 to -30 for adipose tissue. The cross-sectional areas of subcutaneous adipose tissue, visceral adipose tissue and muscle were normalised for stature ($cm^2/height^2$), and described as subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI) and skeletal muscle index (SMI) [22].

Statistical analysis

All continuous data were assessed for normality using a Shapiro-Wilk test and expressed as mean ± standard deviation, unless otherwise reported. Mann-Whitney U (for continuous, nonnormally distributed data), or independent *t* tests (for continuous, normally distributed data) were used to compare variables associated with hospital admission. Between-group analyses also compared differences in liver disease severity scores, cardiorespiratory fitness and body composition indices between patients where the primary indication for transplant listing was hepatocellular carcinoma. A Kruskal-Wallis test explored the difference in VT, SATI, VATI and SMI between those who had 0, 1 or 2 sepsis-related hospital admissions. Post hoc pairwise comparisons were performed using Dunn's method with Bonferroni corrections to account for multiple comparisons. Multivariate logistic regression examined the associations between the development of sepsis and clinically relevant predictors, including patient age (in years), MELD-Na score at the time of CPET, diagnosis of HCC, presence of ascites, use of beta-blocker medication, and the VT. These variables were also used as exposures in a multivariate Poisson regression to

calculate the incidence rate ratios for developing 1 or more episodes of sepsis requiring hospital admission from the time of listing until death, removal from the waiting list, liver transplantation or the final date of data collection (June 2015). Patient waitlist duration was used as the offset variable in the model. To determine whether associations between VT and hospital admission were specific for sepsis, the analysis was also undertaken for all hospital admissions and unplanned admissions for other complications of advanced liver disease, specifically hepatic encephalopathy, variceal bleeding and fluid overload. Finally, a receiver-operator characteristic (ROC) curve was performed using VT to determine the accuracy of predicting sepsis-related hospital admission. The optimal-cut off value with the highest sensitivity and specificity for VT was determined as the value closest to the upper left corner on the plot. All analyses were performed using a statistical software package (SPSS, Version 24, IBM, New York, USA) and statistical significance was assumed if $P < 0.05$.

RESULTS

Patient characteristics

There were 126 consecutive patients listed for liver transplantation during the study period. Patients with cholestatic liver disease (n = 18); those listed for acute liver failure (n = 9); or who did not perform a CPET (n = 12); and those with incomplete CPET or CT data (n = 5) were excluded. Eighty-two patients who performed a CPET as part of their evaluation prior to liver transplantation were included in the analysis. Seven patients were subsequently delisted, 5 patients because they deteriorated and were deemed too sick for transplant, and 2 due to progression of their HCC. No patient was delisted due to a poor VT. The majority of patients were male (87%) and approximately half the cohort had radiologically-diagnosed hepatocellular carcinoma

(45.1%) as the primary indication for liver transplantation. The median age (interquartile range) was 55.1 (50.6 – 59.4) years and MELD-Na score was 18 (13.8 – 22.0). Viral hepatitis was the most frequent cause of chronic liver disease (48.8%), followed by alcohol (36.6%), and then genetic or lifestyle-related conditions (eg, nonalcoholic fatty liver disease) (14.6%). Gastroesophageal varices were present in 78.0% of the patients at the time of CPET. There were 3 patients with hepatopulmonary syndrome and 1 with mild portopulmonary hypertension in the cohort. The majority of the cohort (80.5%) underwent liver transplantation during the data collection period. Seven patients were delisted (8.5%) and a further 9 (11%) remained on the waitlist at the end of the study period. There were no deaths.

There were fifty unplanned hospital admissions in thirty-one patients prior to liver transplantation, with multiple unplanned admissions in 14 patients (10 patients had 2 admissions, 3 had 3 admissions, and 1 patient had 4 admissions). There were twenty-seven admissions for complications of advanced liver disease: twelve patients had fifteen admissions with fluid overload (ascites/hydrothorax/oedema) or complications of managing this (hyponatraemia, postural hypotension); 10 patients had 1 admission each for hepatic encephalopathy, and 2 patients were admitted once after variceal haemorrhage. Sixteen hospital admissions in thirteen patients were for sepsis, including 3 patients with 2 episodes each. The remaining 7 unplanned admissions were for abdominal pain and a clinical concern about possible spontaneous bacterial peritonitis in 2 patients; and 1 patient each with symptomatic portal vein thrombosis, nephrolithiasis, seizures, falls, and diarrhea.

The nature of the septic episodes included spontaneous bacterial peritonitis (n = 6), positive blood cultures (n = 3), urinary tract infection (n = 2) and Campylobacter enteritis (n = 2). The remaining episodes were single events that included cellulitis (n = 1), aspergillus pneumonitis (n = 1) and a lower respiratory tract infection (n = 1). Three patients had 2 separate admissions with sepsis. These infective episodes were due to 2 episodes of spontaneous bacterial peritonitis in 1 patient, 2 urinary tract infections in the second patient, with the final patient having an episode of spontaneous bacterial peritonitis and another of aspergillus pneumonitis. Twelve patients received secondary prophylaxis with antibiotics to prevent recurrent infection. Five of these 12 patients developed an episode of sepsis requiring hospital admission.

Patients diagnosed with sepsis had significantly lower serum sodium (P = 0.02), significantly higher bilirubin (P = 0.009) and MELD-Na score (P = 0.03), and were more likely to have documented ascites (P = 0.049) (**Table 1**). No significant differences were found between the groups for the remaining demographic and clinical characteristics.

There were no adverse events during CPET that required hospitalisation or medical assistance. The median VT for the cohort was 11.7 (9.7 – 13.4) $mL \cdot kg^{-1} \cdot min^{-1}$. The average VT for patients with diagnosed hepatopulmonary syndrome or portopulmonary hypertension was 12.2 $mL \cdot kg^{-1} \cdot min^{-1}$. Patients who developed a septic episode had a significantly lower VT [9.5 (7.8 – 11.9) $mL \cdot kg^{-1} \cdot min^{-1}$] than those who did not develop sepsis [11.8 (10.5 – 13.8) $mL \cdot kg^{-1} \cdot min^{-1}$] ($P$ < 0.01). There was also a significant difference in the VT based on the number of septic episodes (P =

0.01). Patients who were receiving beta-blockers at the time of CPET had a significantly lower VT [10.5 (9.0 – 13.3) $mL \cdot kg^{-1} \cdot min^{-1}$], compared to those who were not taking the medication [12.3 (10.9 – 13.7) $mL \cdot kg^{-1} \cdot min^{-1}$] ($P = 0.017$).

There were 23 patients with CP–A cirrhosis. Four patients with CP-A cirrhosis had a VT ≤ 10 $mL \cdot kg^{-1} \cdot min^{-1}$, with one of these patients admitted for sepsis. HCC patients also had a significantly greater VT (13.2 ± 3.6 $mL \cdot kg^{-1} \cdot min^{-1}$) compared to patients without a HCC (11.1 ± 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$) ($P < 0.01$) (**Table S1, http://links.lww.com/TP/B602**). However, 3 patients with HCC had 4 admissions for sepsis. One patient had 2 admissions for UTI's; another was admitted for a LRTI; while the final patient had a positive blood culture with unknown cause. All causes of sepsis were independent of loco regional treatment (TACE or RFA) for HCC.

There were no significant correlations between CT-derived measures of body composition and admissions for sepsis, variceal haemorrhage, fluid overload, or for any other unplanned admission. Patients admitted for hepatic encephalopathy had significantly greater SATI ($P < 0.01$) and VATI ($P = 0.02$), but not SMI ($P = 0.12$). No correlations between body composition variables and the number of admissions for sepsis were found.

Multivariate logistic regression revealed that the VT was independently associated with the development of sepsis (Odds ratio = 0.675, 95% CI = 0.471 – 0.965, $P = 0.03$). The VT was not significantly associated with admissions for variceal haemorrhage, fluid overload, hepatic encephalopathy, or any other indication.

Multivariate analysis incorporating individual body composition variables into the model revealed that SATI ($P < 0.01$), VATI ($P = 0.04$) and SMI ($P = 0.024$) were associated with admissions for hepatic encephalopathy. When all body composition parameters were included in the same model, only SATI retained significance (Odds ratio = 1.033, 95% CI = 1.003 – 1.063, $P = 0.03$). There were no associations found between body composition measures and admissions for sepsis, variceal haemorrhage, fluid overload or other indications.

Results of the multivariate Poisson regression analysis adjusted for liver transplant waitlist duration are shown in **Table 2**. Pretransplant VT remained the only significant predictor of number of septic episodes ($P = 0.02$). This was independent of age, MELD-Na score, HCC diagnosis, presence of ascites, and the use of beta-blocker prophylaxis.

Prediction of a sepsis-related hospital admission using VT

ROC curve analysis of VT to predict sepsis demonstrated 69.2% sensitivity and 81.2% specificity, with the area under the curve calculated as 0.76 [95% CI 0.599 – 0.913 ($P < 0.01$)] (**Figure 1**). The optimal cut-off value of VT to identify patients who went on to develop a septic episode was ≤ 10.0 $mL.kg^{-1}.min^{-1}$, with 9 (69.2%) of thirteen patients admitted with sepsis having a VT ≤ 10.0 $mL.kg^{-1}.min^{-1}$ (**Figure 2**).

DISCUSSION

This is the first study to examine the relationship between cardiorespiratory fitness and the development of complications of liver disease requiring hospital admission in patients awaiting liver transplantation. The main finding was that the VT was

associated with the development of clinically significant infections, independent of age, MELD-Na score, HCC diagnosis and the presence of ascites in patients with advanced liver disease. The patients who experienced a septic episode had significantly lower VTs compared to those who did not. There was no association between measures of muscle mass or central obesity and the subsequent development of sepsis requiring hospital admission. These data emphasise the utility of assessing cardiorespiratory fitness using VT to identify patients with advanced liver disease who are at an increased risk of developing sepsis.

CPET provides valuable insight into a patient's cardiopulmonary reserve to cope with physiological stresses such as infection. Poorer cardiorespiratory fitness prior to liver transplantation is associated with higher peri-transplant morbidity and mortality [7,9]; while physical inactivity has been shown to correlate with the risk of sepsis in the general population [23]. However the relationship between cardiorespiratory fitness and complications prior to liver transplantation is relatively unexplored. Ow and colleagues recently examined the prognostic value of CPET in predicting 30- and 90-day waitlist mortality [24]. They found that patients with a UK Model for End-Stage Liver Disease (UKELD) score $\geq$ 57 and peak $\dot{V}O_2 \leq 17.6$ mL.kg^{-1}.min^{-1} had a 38% higher risk of mortality compared to those with peak $\dot{V}O_2 > 17.6$ mL.kg^{-1}.min^{-1}, with sepsis accounting for 30% of the waiting list deaths. Although there were no deaths in our cohort, the association between a low VT and a greater incidence of sepsis reported here may in part explain the increased mortality reported in this previous investigation.

The specific mechanisms linking impaired cardiorespiratory fitness and increased risk for sepsis are currently unknown. Patients with advanced liver disease may exhibit ventilation-perfusion mismatching and tissue hypoxemia as a result of vasodilation and arteriovenous shunting [25-27]. An impaired ability to augment tissue oxygen delivery in cirrhosis might increase the risk of bacteria translocation from the gut, causing clinically significant infections [28]. As well as increasing the risk of infection, these changes may reduce the effectiveness of innate immune responses to clear infections.

Sarcopenic obesity has previously been shown to be associated with a greater incidence of sepsis-related mortality in patients with cirrhosis [15]. This relationship has been attributed to protein malnutrition and liver disease-related irregularities in energy metabolism [29]. Low muscle mass may contribute to a reduced reserve to tolerate physiological stressors [30,31], while visceral adipose tissue is associated with increased inflammatory and oxidative stress biomarkers [16]. However, we found no significant differences in SMI and VATI between patients who did or did not develop an episode of sepsis.

Although the data presented here highlights that cardiorespiratory fitness appears to have utility in identifying those at increased risk of developing sepsis, there is overlap with the VT of some of the patients who did not develop sepsis. Because of this overlap, the data presented here do not support the use of antibiotic prophylaxis in patients with a low VT. Nonetheless, it would be important to further understand the physiological mechanisms linking cardiorespiratory fitness and infection risk. Furthermore, it would also be logical to investigate whether interventions known to

increase cardiorespiratory fitness such as exercise training may reduce the incidence of sepsis, and improve pre, peri- and postoperative outcomes in patients with advanced liver disease.

There is currently a paucity of randomised-controlled trials evaluating an exercise training intervention in patients with decompensated liver disease. Moreover, mixed results have been reported in the small number of clinical trials that have examined the efficacy of moderate continuous exercise training to improve cardiorespiratory fitness in compensated cirrhosis [32-34]. These inconsistent findings are likely due to small sample sizes, and require further validation in a larger cohort with decompensated liver disease.

A limitation of this investigation was the retrospective study design and also the relatively small sample size to evaluate the association between CPET variables and clinical outcomes. Additionally, all body composition variables were analysed from a single CT slice, normalised for patient height. This approach does not include the potential influence of appendicular fat or muscle on the risk of sepsis. Nonetheless, single slice CT or MRI evaluations of muscle and fat are widely used and accepted measures of body composition.

In summary, we report evidence that cardiorespiratory fitness (as measured by VT) in patients with advanced liver disease appears to protect patients from severe sepsis; and that CPET can identify patients at increased risk of sepsis-related hospitalisation. This may have implications for using CPET results in prioritizing organ allocation to patients on a liver transplant waiting list. In addition to validating this finding in other

cohorts at risk of sepsis, exercise training should be investigated to determine if improving VT reduces the risk of sepsis in patients with advanced liver disease.

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Figure 1. Sensitivity and specificity analysis of ventilatory threshold for predicting the diagnosis of sepsis. Optimal ventilatory threshold ≤10.0 $mL.kg^{-1}.min^{-1}$, area under the receiver operator characteristic curve = 0.74, 95% CI = CI 0.568-0.921, $P < 0.01$)

Figure 2. Plot of the ventilatory threshold versus the diagnosis of a septic episode prior to liver transplantation. Circles represent a ventilatory threshold ≤ 10 $mL.kg^{-1}.min^{-1}$. Squares represent a ventilatory threshold > 10 $mL.kg^{-1}.min^{-1}$.

Figure 1

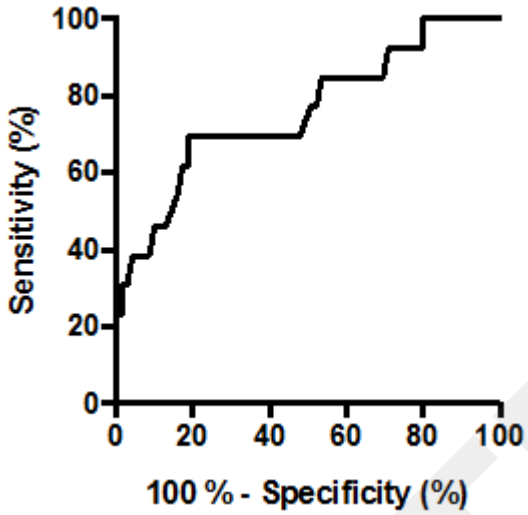

Figure 2

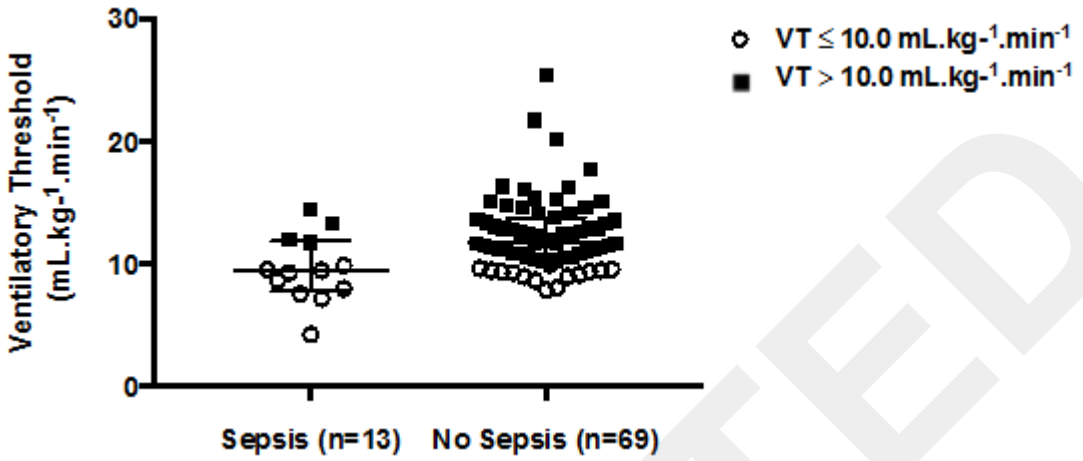

Table 1. Demographic, laboratory, cardiopulmonary exercise testing and body composition data of patients with advanced liver disease who either had, or did not have a septic episode prior to liver transplantation

	Overall (n=82)	Sepsis (n=13)	No Sepsis (n=69)	*P* value
Demographics				
Age (years)	55.1 (50.6-59.4)	53.4 (50.1-57.9)	55.5 (50.5-59.5)	0.37
Sex: male [n (%)]	71 (86.6%)	12 (92.3%)	59 (85.5%)	0.51
Etiology [n (%)]				
Viral	40 (48.8%)	6 (46.2%)	34 (49.3%)	0.84
Alcohol	30 (36.6%)	5 (38.5%)	25 (36.2%)	0.88
Other	12 (14.6%)	2 (15.4%)	10 (14.5%)	0.93
MELD-Na score	18.0 (13.8.0-22.0)	21.0 (18.0-26.5)	17.0 (13.0-22.0)	0.03
Child-Pugh score	9 (6-10)	10 (8.5-12)	8 (6-10)_	0.02
Child-Pugh class (A/B/C)	23/27/32	1/4/8	22/23/24	0.12
HCC: yes [n (%)]	37 (45.1%)	3 (23.1%)	34 (45.1%)	0.08
Waitlist time (days)	84.5 (35.5-160.3)	110.0 (47.0-195.0)	82.0 (33.5-154.0)	0.31
Ascites: yes [n (%)]	49 (59.8%)	11 (84.6%)	38 (55.1%)	0.049
Gastroesophageal varices: yes [n (%)]	64 (78.0%)	9 (69.2%)	55 (79.7%)	0.40
Beta-blockers: yes [n (%)]	35 (42.7%)	8 (61.5%)	27 (39.1%)	0.13
Laboratory				
Sodium (mmol/L)	136.0 (132.8-138.0)	132.0 (129.0-136.5)	136.0 (133.5-138.0)	0.02
Creatinine (µmol/L)	73.0 (58.5-93.25)	78.0 (62.0-108.0)	73.0 (57.5-91.5)	0.18
Bilirubin (µmol/L)	40.0 (29.8-70.0)	64.0 (44.0-97.0)	37.0 (24.5-65.0)	0.009
Platelet count ($x10^9$/L)	76.0 (57.3-123.3)	89.0 (55.0-114.0)	74.0 (57.5-125.5)	0.94
Albumin (g/L)	30.0 (26.0-37.0)	28.0 (23.5-34.5)	30.0 (26.0-37.0)	0.39
Alanine transaminase (U/L)	51.0 (29.8-96.3)	36.0 (25.5-86.0)	51.0 (32.0-96.5)	0.40
Aspartate aminotransferase (U/L)	76.0 (53.5-144.5)	73.0 (56.5-145.5)	77.5 (53.0-145.3)	0.91
Gamma-glutamyl transferase (U/L)	47.0 (32.8-77.3)	43.0 (23.5-55.0)	50.0 (34.5-80.0)	0.26
Alkaline phosphatase (U/L)	111.5 (88.8-143.0)	123.0 (95.0-183.5)	110.0 (88.5-139.0)	0.24
CPET variables				
VT ($mL \cdot kg^{-1} \cdot min^{-1}$)	11.7 (9.7-13.4)	9.5 (7.8-11.9)	11.8 (10.5-13.8)	0.003
Body composition measures				
SATI ($cm^2/height^2$)	57.1 (39.5-79.2)	59.9 (40.2-95.0)	56.5 (39.3-78.7)	0.52
VATI ($cm^2/height^2$)	42.8 (27.1-60.2)	35.6 (24.1-48.2)	44.0 (27.3-61.0)	0.27
SMI ($cm^2/height^2$)	52.0 ± 8.6	50.2 ± 7.5	52.3 ± 8.8	0.41

Values presented as mean ± SD, or median (interquartile range) where data were not normally distributed, unless otherwise stated. MELD-Na = model of end-stage liver disease, incorporating serum sodium; HCC = hepatocellular carcinoma; CPET = cardiopulmonary exercise testing; VT = ventilatory threshold; SATI = subcutaneous adipose tissue index; VATI = visceral adipose tissue index; SMI = skeletal muscle index

Table 2. Incidence rate ratios (IRR) for overall sepsis diagnoses prior to liver transplantation

Variable	IRR	95% CI	*P* value
Age (years)	0.992	0.938-1.049	0.79
MELD-Na score	1.052	0.907-1.219	0.51
HCC (yes)	1.427	0.400-5.082	0.58
Ascites (yes)	0.767	0.179-3.293	0.85
Beta-blockers (yes)	0.940	0.302-2.929	0.92
VT ($mL.kg^{-1}.min^{-1}$)	0.769	0.622-0.951	0.02

MELD-Na = model of end-stage liver disease, incorporating serum sodium; HCC = hepatocellular carcinoma; VATI = visceral adipose tissue index; SMI = skeletal muscle index; VT = ventilatory threshold